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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,549	06/07/2001	John SantaLucia JR.	WSU 0192 PUSP	7537

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EXAMINER	
LIN, JERRY	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,549	SANTALUCIA ET AL.	
	Examiner	Art Unit	
	Jerry Lin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-18,20,21,24-37,39-41,44-57 and 59-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-18,20,21,24-37,39-41,44-57 and 59-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments, filed February 27, 2006, have been fully considered and they are not deemed to be persuasive. The following rejections are reiterated. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, 2nd paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 61-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claims 61 – 63 were amended to include the limitation of linear correction data for hybridization to DNA micro chips. It is unclear if the nucleic acids are hybridizing to the microchip itself (e.g. the solid support or substrate), or if the nucleic acids are hybridizing to bound nucleic acids on the microchip. For purposes of this examination, it will be assumed that the nucleic acids are hybridizing to the bound nucleic acids on a microchip.

This rejection is necessitated by amendment.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 4, 5, 9-18, 20, 21, 24, 25, 29-37, 39-41, 44, 45, 49-57, and 59-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lange et al. (US 6,403,314) in view of Lane et al. (US 6,027,884).

The instant claims are drawn to a method predicting nucleic acid hybridization thermodynamics in a solution that includes providing a database of thermodynamic parameters, receiving hybridization information, receiving correction data, receiving a first set of data that represents hybridization conditions, calculating nucleic acid hybridization thermodynamics, and calculating equilibrium concentration.

Regarding claims 1, 21, 39, 41, and 59, Lange et al. discloses a method of predicting the nucleic hybridization in a solution (column 1, lines 15-25; column 3, lines 5-24) which includes providing a database of thermodynamic parameters (column 15, lines 45-58); receiving hybridization information that represents at least one target

sequence and a primer and a probe wherein the target sequence is longer than the length of the primer and probe (i.e., a probe hybridizing within a target molecule) (column 16, lines 1-60; column 3, line 62-column 4, line 59; Figures 5B and 5C; column 5, lines 25-63; column 7,lines 16-29); calculating nucleic acid hybridization thermodynamics including net hybridization thermodynamics based on hybridization information, thermodynamic parameters, hybridization conditions, and correction data (column 11, lines 39-55, column 15, lines 46-58); wherein the correction data includes folding correction data that includes free energy values and enthalpy values (column 15, lines 4-12 and 42-68); wherein the nucleic acid hybridization thermodynamics are calculated for a best target/primer or target/ probe complex and for competitive mismatch complexes (column 5, lines 47-63). Furthermore, Lange et al. teach implementing their method using C++ pseudo-code, which would require the use of a computer systems as well as a computer readable storage medium (column 16, line 61-column 17, line 8).

Lange et al., however, do not teach where the first set of data, which represents hybridization conditions, is received, or calculating an equilibrium concentration for a species of a molecular complex at a plurality of temperatures, or outputting the equilibrium concentration to an interface.

Also regarding claims 1, 21, 39, 41 and 59, Lane et al. teach a method of determining the thermodynamics of hybridization that includes receiving correction data such as receiving singlet and doublet values to input into a correction factor (column 38, lines 14-61); receiving a set of data that represents hybridization conditions (column 45,

lines 21-35; column 48, lines 11-29); calculating an equilibrium concentration for a species of a molecular complex at a plurality of temperatures using statistical weighting and nucleic acid hybridization thermodynamics and outputting the equilibrium concentration (Figure 4, column 9, lines 50-64; column 42, line 43-column 43, line 65).

Regarding claims 11, 31, and 51, Lange et al. teach wherein the thermodynamic parameters include DNA loop thermodynamic parameters (column 15, lines 4-12).

Regarding claims 4, 24, 44, 61, 62, and 63, Lane et al. teach wherein the correction data includes linear correction data (column 52, line 49-column 53, line 16).

Regarding claims 5, 9, 10, 25, 29, 30, 45, 49, and 50, Lange et al. teach wherein the thermodynamic parameters include DNA, RNA, and DNA/RNA thermodynamic parameters (column 15, lines 18-67).

Regarding claims 12, 32, and 52, Lange et al. teach wherein the hybridization information represents a duplex (column 15, line 17- column 16, line 60).

Regarding claims 13-17, 33-37, and 53-57, Lange et al. teach wherein the hybridization information represents at least a section of the target sequence and a length of at least one primer or probe complimentary to at least a section of the target sequence, wherein the nucleic acid hybridization thermodynamics are calculated for a plurality of primers or probes complementary to at least a section of the target sequence, wherein the hybridization information represents at least a section of the target sequence and a primer or probe, wherein the length of at least a section of the target sequence is longer than a length of the primer or the probe (column 15, lines 32-

41; column 16, lines 1-60; column 3, line 62-column 4, line 59; Figures 5B and 5C; column 5, lines 25-63, column 7,lines 16-29).

Regarding claims 20, 40, and 60, Lane et al. teach wherein the thermodynamics are calculated for at least two best target/primer or target/probe complexes and for their corresponding competitive mismatch complexes and correcting for any interactions between at least two best target/primer or target/probe complexes and their components (column 45, lines 7-61).

It would have been obvious to combine the references of Lange et al. and Lane et al. given that both methods are drawn to determining hybridization thermodynamics. One of Lane et al.'s stated goals is to determine the free energy-parameter of a duplex formed by the hybridization of a single stranded nucleotide (column 2, lines 40-43). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to use a method, such as one disclosed by Lange et al., to determine the hybridization potential of two polymers (column 1, lines 15-25). In addition, both methods are implements using computational techniques, which one of ordinary skill in the art may combine with ease. Thus it would have been obvious to one of ordinary skill in the art to combine the methods of Lange et al. and Lane et al. given their common goals and common implementation techniques.

Response to Arguments

6. Applicants have amended instant claims 1, 21, and 41, to include the limitation of receiving folding correction data that includes a free energy value and enthalpy value.

Applicants state that the instant references do not teach this limitation. The Examiner disagrees.

Lange et al. teach taking into account the structure of intervening loops (folding correction data) (column 15, lines 4-12). In order to use the data of intervening loops, Lange et al. must first receive that data. Furthermore, Lange et al. teach that to assess the stability of the fragments nearest neighbor thermodynamics may be used which includes free energy and enthalpy (column, lines 42-68). Thus Lange et al. teach receiving folding correction data that includes free energy values or enthalpy values.

Applicants also state that Lane et al. do not teach the newly added limitation of calculating an equilibrium concentration of each of a plurality of species wherein at least one of the species is a folded species in claims 1, 21, and 41. Applicants state that the art cited by the Examiner is Van't Hoff plots. The Examiner disagrees that Lane et al. do not teach the instant limitation.

Although figure cited by the Examiner is a Van't Hoff plot, the figure also demonstrates the concentration of the strands. Furthermore, Lane et al. also discuss calculating the equilibrium concentration of hybridization (column 54, lines 56-column 55, line 33; column 8, lines 13-65). Lane et al. also conduct their experiments with different molecular complexes including folded molecular complexes (column 42, lines 20-43). Thus Lane et al. also teach this instant limitation.

Applicants also amended claims 61-63 to include the limitation of DNA microchips. Applicants state that Lane et al. fail to mention DNA microchips and do not teach using linear data. The Examiner agrees that Lane et al. do not mention DNA

microchips. However, Lane et al. teach determining the rate of duplex formation (linear correction data for hybridization) (column 27, line 30 – column 28, line 63). It is noted that hybridization to a DNA microchip is not the hybridization of a nucleic acid to the chip itself, rather it is the hybridization of nucleic acids to the bound nucleic acids on the chip. Since Lane et al. teach linear correction data for hybridization, and Lange et al. teach that their instant method is applicable to hybridization arrays, which would include DNA microchips (column 3, lines 23-44), the combination of the Lane et al. and Lange et al. do teach the newly added limitation.

This rejection is necessitated by amendment.

7. Claims 6-8, 26-28, and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lange et al. (US 6,403,314) in view of Lane et al. (US 6,027,884), further in view of Barciszewski et al. (RNA Biochemistry and Biotechnology).

Lange et al. and Lane et al. are applied as above.

Lange et al. or Lane et al. do not explicitly teach using dangling end parameters, coaxial stacking parameters, or terminal mismatch parameters.

Regarding claims 6-8, 26-28, and 46-48, Barciszewski et al. teach using dangling end parameters (p. 21, fourth full paragraph), coaxial stacking parameters (p. 22, first full paragraph), and terminal mismatch parameters (p. 15, third full paragraph).

It would have been obvious to one or ordinary skill in the art to combine the references of Lange et al. and Barciszewski et al. Lange et al. teach a computational

method for predicting the hybridization stability of two polymers (see abstract). Barciszewski et al. also teach a computational method that utilizes the thermodynamics of nucleic acids to determine secondary structure (se abstract). Both method are implemented using computational techniques which one of ordinary skill in the art my combine with ease. Lange et al. further state that their method is extremely flexible and can incorporate many different computational methods (column 6, lines 51-60). In addition, one of Lange et al.'s stated goals is to analyze and list all possible single-fragment and multi-fragment cross-hybridizations between a probe molecules and a target molecule and to find the most stable hybridization (column 5, lines 44-56). To achieve Lange et al.'s stated goals, one of ordinary skill in the art would incorporate the method disclosed by Barciszewski et al. to include polymers with dangling ends or terminal mismatches to expand the types of polymers Lange et al.'s method can analyze to find all the possible hybridizations and to find the most stable duplex.

This rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571) 272-2561. The examiner can normally be reached on 10:00am-6:30pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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MICHAEL BORIN, PH.D
PRIMARY EXAMINER

JL